

Research Protocol

Study Title: A novel approach to optimize Programmed Intermittent Epidural Bolus (PIEB) delivery for labour analgesia

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Background

Labor pain is highly variable, but often described as severe⁽¹⁾, and reported to be the most intense pain that a woman experiences in her lifetime⁽²⁾. Many factors influence labour pain such as parity, the duration of labour, maternal pelvic anatomy, fetal size and presentation, gestational age at birth, labour induction or augmentation and the presence of support^(1, 3, 4). Pain and pain relief are often mentioned as important contributors to women's birth experience⁽⁵⁻⁸⁾. The ideal pain relief method must be safe, effective, timely, efficient, equitable, women-centered and should not interfere with labour or the mobility of the labouring woman⁽⁹⁾. Epidural analgesia is the most effective form of pain relief for women in labour^(10, 11). Previously, the practice was maintenance of labour epidural analgesia through a pump to deliver local anesthetic in combination with an opioid via a continuous epidural infusion (CEI)⁽¹²⁾. Commonly utilized maintenance solutions for CEI include the local anesthetics bupivacaine (0.0625-0.125%) or ropivacaine (0.1-0.16%) combined with sufentanil (0.5-0.75 ug/mL) or fentanyl (2-3 ug/mL)⁽¹³⁾. Continuous epidural infusion was used at the IWK Health Centre as routine care for labour

analgesia until 2015. The epidural pump dosing parameters can be found in Table 1. Continuous epidural infusion was used with patient-controlled epidural analgesia (PCEA) for breakthrough pain. PCEA allows the patient to deliver small doses of the anesthetic solution to supplement the ongoing epidural infusion. The PCEA bolus dose can be set between 4 and 12 mL, with the most common settings between 5 and 8 mL. The lockout interval can be varied, but usually based around the knowledge that approximately 10 minutes is required for the patient to experience pain relief⁽¹⁴⁾.

Continuous epidural infusion has been associated with an increased risk of assisted vaginal birth (vacuum or forceps delivery)⁽¹⁵⁾ and may cause significant motor block (leg heaviness and weakness that limits the woman's ability to ambulate⁽¹⁶⁾). Motor block can contribute to prolonged labour and a prolonged second stage of labour that has been associated with increased maternal morbidity and operative delivery rates⁽¹⁷⁻²⁰⁾. A woman with significant motor block will require more nursing assistance for toileting, hygiene care and ambulation. A study on the economic implications of various methods of delivery using data from the authors' institution showed that the cost associated with assisted vaginal delivery was significantly more than that of spontaneous vaginal delivery (\$1594 vs. \$1340), and was even higher for cesarean delivery in labour (\$2137)⁽²¹⁾. Thus, the importance of reducing the risk of motor block and operative delivery is evident from both a patient safety as well as an economic standpoint.

Evidence now suggests that providing the local anesthetic and opioid solution as a bolus at regularly timed intervals may allow better pain management⁽²²⁻²⁴⁾. The pressure generated by injecting a bolus produces a more uniform spread of solution within the epidural space compared to a continuous infusion. The ability to deliver regularly timed manual doses is labour intensive and not feasible on a busy obstetrical unit. Recent advances in epidural pump technology allows for programmed intermittent epidural bolus (PIEB) administration. In November 2012, Health Canada approved PIEB combined with PCEA (CADD®-Solis Epidural Pump, Smiths Medical, St. Paul, MN, USA) for clinical use. PIEB for labour analgesia allows the epidural pump to be programmed to deliver small amounts of the local anesthetic and opioid solution at regularly timed intervals; a process that mimics manual doses delivered by an anesthesia provider. The programmer can specify the volume of medication to be provided as a bolus and the timing

between the boluses. The patient can also use the PCEA button to administer an additional dose of the same medication at their discretion. A “lockout” interval is programmed for the PCEA to ensure there is not an overdose of medication that may lead to motor block and hypotension (Figure 1). In 2015 at the IWK Health Centre, PIEB replaced CEI as routine care for the delivery of labour analgesia. Table 1 lists the PIEB pump setting used at the IWK Health Centre for PIEB. The attending anesthesiologist has the ability to alter the settings provided the settings are still within the predefined safety parameters. The pump settings are verified by nursing staff to further ensure patient safety.

Early studies found clinical advantages of PIEB when compared to a continuous infusion^(22, 23, 25-30). George *et al.* completed a systematic review in 2013, which highlighted that PIEB delivery was associated with several important outcomes including: improved patient satisfaction, reduced local anesthetic consumption, and decreased duration of the second stage of labour⁽¹²⁾. A recent study found that PIEB with PCEA had significantly fewer patients with motor block, a shorter second stage of labour for primiparous women and women received less ropivacaine compared to CEI with PCEA⁽³¹⁾. However, there was no significant difference in mode of delivery or maternal satisfaction in this study⁽³¹⁾.

As health care practices evolve toward patient-centered care and patient engagement, consideration of patient satisfaction with their labour analgesia is paramount. Capogna *et al.* designed a study to detect a difference in instrumental delivery rates reported a significant reduction with PIEB compared with CEI (7% vs 20%; $P = 0.03$)⁽²²⁾. The authors attribute the higher rates of instrumental delivery to greater motor blockade present in the CEI group. Further support for the reduction in total local anesthetic consumption using PIEB for labour analgesia is observed when evaluating the need for rescue clinician boluses. The occurrence of breakthrough pain may be treated with a dose of local anesthetic, known as a rescue bolus, supplied manually by a member of the anesthesia team (anesthesiologist, anesthesia assistant or anesthesia resident). The need for a rescue bolus results in increased demand for anesthesia clinical services and may lead to a delay in pain relief for the patient if the clinician is not readily available. While an earlier systematic review did not find a significant difference in the need for clinician top-up bolus between PIEB and CEI, more recent studies have shown different results^(12, 32, 33). Both

studies by MacKenzie et al. and Delagado et al. have demonstrated less need for epidural top-ups with the use of PIEB. The study examining programmed bolus of 10ml bupivacaine 0.0625% with fentanyl 2mcg/ml every 45 or 60 minutes or every 45 min with high flow (500 ml/hour)⁽³³⁾ found the top-up rate was lower in the 45 minute interval group compared with the 60 minute interval group⁽³³⁾.

Despite its growing use as the routine care for delivery of labour analgesia, and adoption at the IWK Health Centre, little evidence is available to guide optimal settings for PIEB. The gaps in evidence include: (1) programmed timing for the first PIEB bolus (referred to as the “NEXT bolus”) (2) determination of PIEB bolus volume (3) the interval for subsequent doses (PIEB interval). Figure 1 outlines the functions of the PIEB pump. When an epidural is initiated, the clinician provides the first dose manually through the epidural catheter. The epidural catheter is then connected to the PIEB pump, and the pump is programmed according to the current institutional settings (Table 1). Once programmed, 15 minutes later the first pump-delivered dose, known as the “NEXT Bolus” is provided, followed by a programmed dose every 45 minutes (Figure 1). This 45-minute interval between regular boluses is known as the PIEB interval. If patients require additional pain control, they are able to press a button to receive a rescue PCEA bolus (6mLs) every 10 minutes. This timing can also be adjusted, and is known as the “PCEA lockout”. If a patient presses the PCEA button requesting a bolus within this lockout time period, the pump records the request but does not administer a dose.

PIEB offers an advantage, given the customizability of the various parameters, to reduce patient complications, increase pain control, and increase patient satisfaction. However, clinical practice has seen large variation in PIEB pump parameters and there has been no consensus in dose, volumes and intervals amongst the randomized trials^(12, 31, 34). The timing for the NEXT bolus has been varied between 15 and 45 minutes. Similarly, previous research has suggested a PIEB interval between 15 to 60 minutes⁽³¹⁾. Lastly, optimal PIEB volume has had very little research but available studies used volumes that range between 2.5 to 10 mL of a local anesthetic and opioid solution^(30, 31). The PCEA bolus and lockout interval have been maintained at similar volume and intervals used with traditional labour epidural pumps^(31, 35).

Choosing the parameters for the pump has implications for patient safety (risk of hypotension and motor block) and patient satisfaction. A fine balance is required in choosing the settings for PIEB delivery, as each extreme has its own disadvantages. A small bolus volume with a short interval may be associated with similar drawbacks mentioned for continuous epidural infusions, while a large volume bolus with a longer interval may be associated with breakthrough pain and reduced patient satisfaction⁽³⁶⁾. Longer intervals between PIEBs may mean that overall, more local anesthetic and opioid is consumed in the form of PCEA or clinician administered manual boluses for inadequate pain control. More local anesthetic could contribute to a sudden decrease in blood pressure or greater motor blockade⁽¹¹⁾. Despite the obvious need to determine the optimal setting for these PIEB variables, few studies have been designed to evaluate this question.

An early study by Wong *et al.* randomized patients to one of three PIEB dose regimens for maintenance of analgesia: 2.5 mL every 15 minutes (2.5/15), 5 mL every 30 minutes (5/30), or 10 mL every 60 minutes (10/60). The study showed that extending the PIEB interval from 15 min to 60 min with a larger PIEB volume (10 mL vs. 2.5 mL) resulted in decreased anesthetic consumption without affecting patient satisfaction⁽³⁶⁾. This finding complemented previous work which suggested that larger boluses with a longer lockout interval may improve spread of the local anesthetic and opioid solution in the epidural space leading to superior analgesia⁽¹³⁾. Another study was designed to establish the optimal time interval between boluses (PIEB interval) using 10 mL of bupivacaine 0.0625% with fentanyl 2 µg/mL to produce effective analgesia in 90% of women during first stage of labour⁽³⁷⁾. This study was a double-blind sequential allocation trial with a biased-coin up-down design with the PIEB interval set at 60 minutes for the first patient and at varying time intervals (60, 50, 40, and 30 minutes; groups 60, 50, 40 and 30, respectively) for the subsequent patients. The primary outcome was effective analgesia, defined as no requirement for PCEA or a manual bolus for 6 hours after the initiation of the epidural analgesia or until the patient was fully dilated. The author's found that the optimal PIEB interval was approximately 40 minutes.

The study by Delagado *et al.* examining programmed bolus of 10ml bupivacaine 0.0625% with fentanyl 2mcg/ml every 45 or 60 minutes or every 45 min with high flow (500 ml/hour)⁽³³⁾ found

the manual bolus rate was lower in the 45 minute interval group compared with the 60 minute interval group⁽³³⁾. This information helps to further determine the optimal PIEB interval. However, despite their findings the authors concluded that additional parameters need further testing such as the interval between the intrathecal dose and the delivery of the first programmed bolus (NEXT bolus), the volume of the programmed bolus, the interval between programmed boluses, the volume of the patient-controlled bolus (PCEA bolus) and the flow at which all boluses are delivered⁽³³⁾.

Current PIEB studies are only applicable to the corresponding institutes and specific for their standard epidural solution. Additionally, many of the aforementioned studies have evaluated one or two PIEB variables, but have not evaluated how the three main PIEB settings work together, and how they can be optimized to improve patient satisfaction and pain control and to reduce clinical work load. Key issues identified in existing studies that evaluate success with PIEB include reliance on singular assessments of pain with unidimensional tools such as Visual Analog or Numeric Rating Scales (NRS). Choosing a single outcome as the method of assessment ignores the multidimensional nature of women's pain and may be associated with lower levels of reliability and a ceiling effect to measurement^(38, 39). The latter is demonstrated clinically by reports of labour pain that exceed the upper anchors of these scales (i.e., pain greater than 10/10)⁽⁴⁰⁾. To address this, the authors propose a novel approach to determine the optimal PIEB settings as evaluated by three predefined outcomes: maternal satisfaction, need for clinician rescue bolus, and ratio of PCEA requested doses to PCEA delivered doses. A multivariate design will reduce time, effort, and resources compared to univariate procedures that are traditionally employed in this field of research.

The optimal labour analgesia PIEB pump settings will be estimated using an established mathematical technique known as Response Surface Methodology (RSM). RSM is a collection of statistical and mathematical techniques used with a sequence of designed experiments to obtain an optimal response. Box–Behnken designs (BBD) are specific experimental designs of RSM that are frequently applied to the optimization of analytical methods. RSM selects the optimal combination of several factors to maximize or minimize the effect on a single or multiple outcomes. The technique has been used for analytical applications in the industrial

world and in bioprocesses. The main purpose is to discover conditions which produce the best possible performance. RSM will be used to analyze the influence and importance of several explanatory variables (the PIEB pump settings) on the three response variables (maternal satisfaction, need for clinician rescue bolus, and ratio of PCEA delivered doses to requested doses) (Figure 2)⁽⁴¹⁾. The results of this study will generate an algorithm that identifies optimal PIEB settings that will be generalizable to institutions across Nova Scotia, nationally and in other countries using PIEB for the maintenance of labour analgesia.

OBJECTIVE: To use Response Surface Methodology to best estimate the optimal PIEB settings (NEXT bolus interval, PIEB interval time, PIEB volume) by using the following clinical primary outcome measures: maternal satisfaction score, need for a clinician administered rescue bolus, and the ratio of PCEA boluses requested/delivered.

HYPOTHESIS: Response Surface Methodology will reliably determine the optimal timing and volume of labour analgesia. The optimal system will result in higher patient satisfaction, reduced anesthesia interventions, and improved ratio of requested to delivered PCEA boluses.

METHODS

This study is a randomized trial of predetermined combinations of PIEB pump settings. After administration of an epidural, participating women will be randomly assigned by computer generation to a combination of PIEB settings (Table 2). The participants nurse will be recording safety information during the duration of the epidural. Outcome data for clinical outcomes will be gathered by the research coordinator after delivery. Data will be retrieved from the epidural pump, the anesthesia database Innovian (Draeger, Inc. Telford, USA) a web-based information management system that creates a complete, continuous, paperless record of patient's anesthetic care) and IntelliSpace Perinatal software (Phillips Medical Systems, Koninklijke Philips N.V.) an electronic comprehensive patient documentation and data storage of obstetrical care. In addition, a patient satisfaction numeric rating scale will be completed by a research coordinator within 24 hours of delivery. Monitoring for patient safety and side effects will be completed by birth unit nurses as part of the routine standard of epidural analgesia care.

Inclusion/Exclusion Criteria

Inclusion Criteria: Nulliparous, English speaking, aged 18-45 years, single gestation ≥ 37 weeks, vertex presentation, American Society of Anesthesiologists (ASA) Physical Status II (mild and controlled systemic disease and/or pregnancy)⁽⁴²⁾, requesting an epidural for labour analgesia, cervical dilation ≤ 7 cm at the time of initiation of epidural analgesia.

Exclusion Criteria: Preeclampsia or HELLP syndrome, maternal cardiac disease, severe or uncontrolled maternal systemic disease, contraindication to neuraxial analgesia (i.e. coagulopathy, infection, neuropathy), abnormal spinal anatomy (i.e. severe scoliosis, spina bifida, spinal instrumentation), chronic analgesic use, a physical or psychiatric condition which may impair cooperation, known fetal anomalies/intrauterine fetal demise, height $< 5'0''$, Body Mass Index $> 45 \text{ kg/m}^2$,

Withdrawal Criteria: Failure to establish epidural analgesia, failure to insert epidural catheter, intrathecal or intravenous epidural catheter, delivery within 180 minutes of study commencement.

Procedures

Potential participants will be identified by research personnel by communicating with the attending anesthesiologist on the Birth Unit, the Birth Unit charge nurse, and nurses in the Early Labour and Assessment unit at the IWK Health Centre. Nurses will receive education regarding the study as an education session prior to study commencement. The patient's nurse will ask the patient if they would be willing to speak with research staff. With their consent, participants will be approached by study personnel to discuss the study in detail. Inclusion and exclusion criteria will be verified and informed, written consent will be obtained. All participants will be female, as the study is designed for labouring patients. Recruitment on the Birth Unit is standard procedure for labour analgesia research.

As standard care in the Birth Unit, upon request of labour analgesia, the cervix will be measured, a baseline pain score will be determined by Birth Unit nurses and the patients' blood pressure

will be determined. An intravenous catheter will be in place before epidural initiation. A staff anesthesiologist will use an epidural technique to initiate labour analgesia. With the patient in the sitting position, the epidural space will be identified at the L3-4 or L2-3 interspace with a 17G, 9 cm Tuohy epidural needle using a loss of resistance to air or saline (< 1 mL) technique. A multiple-orifice catheter will be inserted five centimeters into the epidural space and a pharmacy prepared bolus of 10 ml ropivacaine 0.2% with 10 ug/ml fentanyl solution will be administered via the catheter. This is the standard initial bolus that all patients with LEA receive. The catheter will then be attached to the CADD-Solis Ambulatory Infusion System[®]. After the epidural catheter is secured, the patient will be placed on their left side for a blood pressure assessment. Data collection will take place in the patient's assigned labour room in the IWK Birth Unit. Patients will not be recruited on Fridays to avoid the inability of collecting the satisfaction score ≤ 24 hours postpartum. The following physiologic assessments will be completed by the nursing staff as routine care for women with epidural analgesia for labour to ensure their safety (Appendix 1):

1. Degree of pain (to determine the need for PCEA or a clinician administered rescue bolus). Completed at baseline and then hourly
2. Highest thoracic dermatome sensory level to pin prick (to determine extent of the epidural block), completed hourly after epidural placement
3. Presence of motor block assessed using Modified Bromage scale⁽⁴³⁾ completed hourly after epidural placement
4. Blood Pressure (measured before epidural placement, then assessed every 5 minutes for three measurements after epidural placement, again at the 30-minute mark and hourly thereafter as per Birth Unit protocol).

Additional data will be collected by the research assistant using information collected from IntelliSpace Perinatal and the CADD Solis Pump:

5. Total local anesthetic dose consumed
6. Total opioid dose consumed
7. Duration of the second stage of labour
8. Mode of delivery including the indication for cesarean delivery

9. Time from epidural to delivery

The standard PIEB settings used at the IWK are included in Table 1. The only difference from standard of care for the delivery of labour analgesia for study participants will be the PIEB pump settings. However, all possible pump settings used for the study are within the safety limits established at the IWK and have been used in clinical research. Each participant will be randomly allocated (by block randomization) to a combination of predetermined PIEB settings for the NEXT bolus interval, PIEB volume, and PIEB interval (Table 2). Once the patient has been consented, the envelope containing the data collection sheet for the nurse will be placed in the participants chart. The Research Assistant will adhere the randomization envelope for anesthesia to the patient's epidural pump. Additionally, the flag indicating that the pump needs to be returned to the anesthesia work room at the end of its use will be adhered to the patient's epidural pump. The patient and nurse collecting data will be blinded to the PIEB setting assignments. The setting assignments will be sealed in sequentially numbered envelopes. When the participant requests their epidural, the sealed envelope will be opened by an un-blinded member of the anesthesia team (anesthesiologist, anesthesia assistant, or anesthesia resident). The anesthesia team member performing the epidural will program the pump with the designated settings. Verification of the pump settings will be achieved by a second un-blinded healthcare member. The pump will be covered to blind investigators, nurses, and participants. The pump will start 5 minutes after the initial epidural manual bolus. The PCEA doses will remain standardized (6 mL ropivacaine 0.1% with 2ug/mL fentanyl every 10 minutes, as required). If after two confirmed PCEA doses the participant's pain is not suitably controlled, the anesthesia team member will be consulted to provide a manual rescue bolus (10 mL of 0.2% ropivacaine or 10 mL clinician bolus of ropivacaine 0.1% with 2ug/mL fentanyl via the CADD®-Solis Epidural Pump).

Following completion of the study procedures, the randomization envelope will be placed into the study package along with the completed data collection sheet. The study package will be returned to the Birth Unit desk to be collected by the Research Assistant. The Research Assistant will also collect the data from the participant's epidural pump. As an incentive for the nursing staff who have collected the data, after every five participants there will be a draw for a \$20 Tim

Horton's gift card.

The following primary outcome measures will be used with RSM to generate the mathematical model for optimizing PIEB settings:

1. Maternal satisfaction score⁽⁴⁴⁾ (quantified as 0-100, where 0 – not satisfied, and 100 – completely satisfied). Optimal response: ≥ 90 ⁽⁴⁵⁾ determined within 24 hours of delivery by the research coordinator. If the patient is discharged home from the Birth Unit before 24 hours postpartum, the research assistant will complete a telephone follow-up for the satisfaction score within 24 hours postpartum.
2. Number of clinician administered rescue boluses or CADD®-Solis Epidural Pump Boluses, recorded in the Innovian anesthesia database, IntelliSpace Perinatal, or CADD®-Solis Epidural Pump. Optimal response: 0 boluses
3. Ratio of the number of PCEA boluses requested to the number of PCEA boluses delivered (Recorded on the CADD®-Solis Epidural Pump during labour and downloaded by research coordinator after delivery). Optimal response: 1 – a larger ratio means the patient requested PCEA boluses but they were not delivered because the pump was in the 10-minute safety lockout period, implying inadequate pain control.

Statistical Analysis Methodology

Box–Behnken designs (BBD) are experimental designs for response surface methodology RSM. BBM are frequently applied to optimize analytical methods due to their advantages such as a reduction in the number of experiments that need be executed resulting in less patient burden and reduced cost. RSM explores the relationships between several explanatory variables and one or more response variables (Figure 2). It allows the development of mathematical models that permit assessment of statistical significance of the factor effects being studied as well as evaluates the interaction effects between the factors. The main concept behind RSM is to use a sequence of designed experiments to obtain an optimal response. The BBD is a spherical RSM design, with all points lying on a surface of a sphere within the set values of our variables (Figure 3: Coordinates A to M). All of the analysis will be managed by our collaborator and biostatistician, Dr. Andreou. Analysis of the model provides an estimate whether the optimum

outcome is located near the design area or further away. A graphical overlay of the contour plots of each individual outcome can then be used to determine the PIEB settings that produce the desired outcomes to deliver optimal labour analgesia.

The minimum and maximum values for each variable have been chosen based on the literature^(12, 36) and clinical experience: NEXT bolus interval: 15 to 45 min; PIEB interval: 40 to 60 min; PIEB volume: 5 to 8 mL. The optimal dose likely falls on the surface of the sphere within this cube (Figure 3). These thirteen coordinates on the surface of the sphere (Table 2) represent combinations of the variables (Figure 3). Simulations of this analysis suggests that 5 patients assigned to each of the twelve surface coordinates and 10 patients assigned to the center (M & N) coordinate (n=70) will predict the optimal dosage plane with a reasonable degree of certainty. An additional patient will be randomized to the twelve surface coordinates and two patients assigned to the center coordinate to account for any potential drop outs. There will be a total number of 84 patients required to complete the study. The power assumption as based on the hypothesis that maternal satisfaction outcome would have a mean difference of 7.10 with a 95% CI of 6.19 to 7.84, anesthesia interventions occurrence would have a median of 1 with an interquartile range of 1-2, and the ratio of the number of PCEA boluses requested to the number of PCEA boluses delivered would have a median of 1.4 and an interquartile range of 1.0 to 2.2.

The sample size estimation was based on a standard error of 2% and a simulation of 70 trials. The power calculation indicates at least 80% of the response surface will be estimated with standard error less than 2%.

Safety and Monitoring

The investigators will forward all concerns to the independent safety committee consisting of Dr.'s P. Bolleddula (Quality Assurance, Women's & Obstetric Anesthesia, IWK Health Centre), G. Dobson (Quality Assurance Officer, Department of Anesthesia, Pain Management, and Perioperative Medicine, QE II Health Sciences Centre) and a member of the Department of Obstetrics and Gynecology, IWK Health Centre, to review.

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None of the study investigators have commercial conflicts to declare.

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Table 1. IWK Health Centre Continuous Epidural Infusion (CEI) and Programmed Intermittent Bolus (PIEB) anesthesia pump parameters

Labour Analgesia Method	Maintenance Solution and rate	Start of maintenance solution	PCEA volume	PCEA interval
CEI until 2015	6 mLs/hr ropivacaine 0.1% with 2 ug/mL fentanyl	Immediately after epidural catheter placement and pump set up	6 mLs ropivacaine 0.1% with 2 ug/mL fentanyl	10 minutes
PIEB from 2015	8 mLs every 45 min ropivacaine 0.1% with 2 ug/mL fentanyl	15 minutes after epidural catheter placement and pump set up	6 mLs ropivacaine 0.1% with 2 ug/mL fentanyl	10 minutes

Table 2. Programmed Intermittent Epidural Bolus (PIEB) Variable Combinations.

Table 1

Coordinate	PIEB "NEXT Bolus" (minutes)	PIEB Interval (minutes)	PIEB Volume (mL)
A	45	50	5
B	45	40	6.5
C	45	50	8
D	45	60	6.5
E	30	40	5
F	30	40	8
G	30	60	8
H	30	60	5
I	15	50	5
J	15	40	6.5
K	15	50	8
L	15	60	6.5
M	30	50	6.5
M2	30	50	6.5

Figure 1. Programmed Intermittent Epidural Bolus (PIEB) Delivery with Patient Controlled Epidural Analgesia (PCEA)

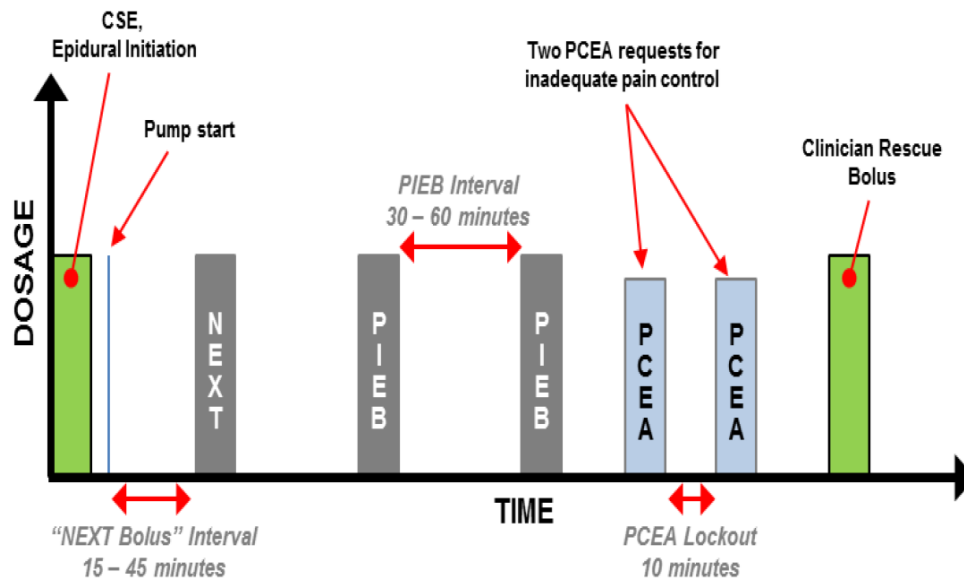


Figure 2. Explanatory and Response Variables for Surface Response Methodology

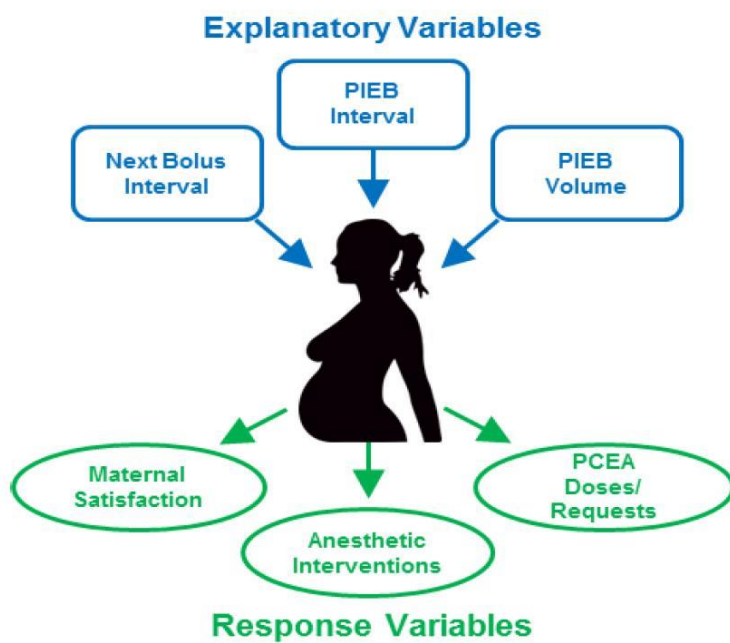


Figure 3. Box-Behnken design (BBD) to predict Optimal Response Surface Methodology (RSM).

